REVIEW

Giant cell arteritis

J M Calvo-Romero

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Giant cell arteritis (GCA), temporal arteritis or Horton's arteritis, is a systemic vasculitis which involves large and medium sized vessels, especially the extracranial branches of the carotid arteries, in persons usually older than 50 years. Permanent visual loss, ischaemic strokes, and thoracic and abdominal aortic aneurysms are feared complications of GCA. The treatment consists of high dose steroids. Mortality, with a correct treatment, in patients with GCA seems to be similar that of controls.

Giant cell arteritis (GCA), temporal arteritis or Horton's arteritis, is a relatively common systemic vasculitis.[1–13] It is a large and medium sized granulomatous arteritis, especially involving the extracranial branches of the carotid arteries.[1 2]

EPIDEMIOLOGY

GCA almost exclusively develops in persons older than 50 years.[1–16] GCA is the most common systemic vasculitis in Western countries.[1–13] The highest incidence rates are described in Scandinavian countries and North American populations of the same descent (table 1). GCA is more common among women than men.[1–13] In the past few years, a progressive increase in the incidence has been reported.[10 11 13]

Table 1 Incidence of giant cell arteritis

Country (date)	Incidence/100000 persons >50 years
Norway (1987–94)	29
Iceland (1984–90)	27
Sweden (1973–75)	18
United States (1950–85)	17
Spain (1988–97)	11
Israel (1980–91)	10
France (1970–79)	9
Italy (1980–88)	7

AETIOLOGY

GCA is a chronic inflammatory disorder targeting large and medium sized arteries. Some familial accumulation and the association with the HLA-DR4 haplotype[8 17 18] indicate a genetic predisposition. Epidemiological observations and some studies using DNA detection techniques suggest an infectious origin (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and parvovirus B19),[19–23] but so far GCA has not been shown to be a truly infectious form of vasculitis. Immunological research demonstrates an antigen-driven disease with local T-cell and macrophage activation in the vessel wall with an important role of the proinflammatory cytokines.[24] The initial process may be a foreign body giant cell attack on calcified internal elastic membrane in arteries and on calcified atrophic parts of the aortic media. The prerequisite of a calcified artery would explain that GCA almost exclusively occurs in persons older than 50 years. Although significant contributions regarding the pathogenesis of GCA are encouraging, the aetiology still remains unknown.

CLINICAL MANIFESTATIONS

Table 2 shows the most common clinical manifestations in four large series. GCA usually begins gradually, but may start abruptly. Although most clinical manifestations of GCA occur before steroid therapy, they may also develop during the early phase of treatment, or during tapering of the dose of steroids.

Constitutional syndrome (asthenia, anorexia, and weight loss) is common.[1–16] Low grade fever (temperature between 37ºC and 38ºC), or inclusive high grade fever (temperature greater than 38ºC), and fever of unknown origin occur in

Table 2 Common clinical manifestations (%) of giant cell arteritis

	Hunder *et al*[89] (n=214)	Baldursson *et al*[7] (n=133)	Armona *et al*[14] (n=191)	González-Gay and García-Porrúa[3] (n=110)
Fever/low grade fever	NR	NR	29	29
Constitutional symptoms	NR	NR	14	14
Headache	64	63	87	87
Abnormal temporal arteries on examination	57	44	75	75
Jaw claudication	41	11	40	40
Amaurosis fugax	28	14	25	25
Irreversible blindness	10	1	12	12
Polymyalgia rheumatica	53	48	49	49

NR, not reported.

Correspondence to:
Dr José María Calvo-Romero, Internal Medicine, Hospital de Zafra, Antigua Ctra Nacional 432, 06300 Zafra (Badajoz), Spain;
jmcromero@eresmas.com

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patients with GCA.[1 2] A new onset or a new type of headache is probably the most common symptom.[1–16] There is carotidynia (pain located at carotid arteries) in some patients. The superficial temporal arteries may be thickened, nodular, tender and erythematous, and pulses may be decreased or absent. Atherosclerosis also causes these temporal artery abnormalities.[25] Occipital, facial, and postauricular arteries are occasionally enlarged or tender.[26] Jaw claudication is frequent, although it is also present in atherosclerosis, amyloidosis, and other vasculitis.[25 27–29] Reduction in jaw opening has been also described.[30] Claudication of the tongue or of swallowing, necrosis of the tongue and scalp, and toothache are uncommon.[31 32] A high frequency of audiovestibular manifestations (nystagmus and hearing loss), which may be reversible after several days of steroid treatment, has been reported in patients with GCA.[33]

Ocular manifestations

Anterior ischaemic optic neuropathy, posterior ischaemic optic neuropathy, central retinal artery occlusion, cilioretinal artery occlusion, amaurosis fugax, eye pain, diplopia, and ocular muscle paresis may occur in GCA.[34–36] Visual ischaemic complications are observed in about 25% of patients with GCA,[37 38] and irreversible visual loss, mainly due to anterior ischaemic optic neuropathy and frequently preceded by amaurosis fugax, is found in 1%–15%.[3 7 14 37–39] Patients with visual ischaemic complications had lower clinical and laboratory biological markers of inflammation.[37–42] Predictors associated with an increased risk of permanent visual loss are a history of amaurosis fugax, jaw claudication, and cerebrovascular accidents, the absence of anaemia, and a higher platelet count.[37–42] The presence of constitutional symptoms, raised liver enzyme levels, or polymyalgia rheumatica has been associated with a reduced risk.[38 42]

Neurological manifestations

Both the central and peripheral nervous system can be involved, resulting in transient ischaemic attacks, ischaemic strokes, dementia, spinal cord infarction, mononeuropathies (for example brachial plexopathy), polyneuropathies, and subarachnoid haemorrhage.[43–49] Ischaemic strokes, affecting carotid or vertebrobasilar territories, are more likely in patients with permanent visual loss or jaw claudication.[42] However, GCA is the aetiology in only a small proportion (about 1%) of the population with ischaemic strokes.[50] Bilateral vertebral artery occlusion is a rare but serious complication of GCA.[51]

Large vessel and other manifestations

Thoracic and abdominal aortic aneurysms, due to aortitis, and dissection are feared complications of GCA.[52–54] Compared with persons of the same age and sex, patients with GCA are 17 times more likely to develop a thoracic aortic aneurysm and 2.4 times more likely to develop an abdominal aortic aneurysm.[53] Aortic valve insufficiency is also possible.[52–54] Lower limb claudication and aortic arch syndrome resulting in arm claudication are important but under-appreciated complications of GCA and may be the presenting feature.[55 56] It has been described that large vessel GCA has a distinct spectrum of clinical manifestations and often occurs without involvement of cranial arteries.[57]

Intestinal infarction, coronary ischaemia, pulmonary artery thrombosis, intra-alveolar haemorrhage, cough, sore throat, hoarseness, peripheral arthritis, haematuria, renal failure, and secondary amyloidosis are possible manifestations of GCA.[16 31 58–64]

Polymyalgia rheumatica

A variable proportion of patients (about 50%) with GCA has polymyalgia rheumatica,[1–16] a clinical syndrome characterised by pain and stiffness in neck, shoulder girdle, and pelvic girdle. A concept is that polymyalgia rheumatica and GCA belong to the same clinical continuum. There is production of cytokines in temporal artery samples of patients with isolated polymyalgia rheumatica.[65 66] Hunder has proposed the term "subclinical" vasculitis to define this finding.[66] However, GCA and polymyalgia rheumatica seem to be distinct conditions. For example, there are differences in the HLA class II associations.[17] Rodríguez-Valverde *et al* described a subset of patients with polymyalgia rheumatica with a very low likelihood of GCA.[67] Patients with polymyalgia rheumatica younger than 70 years and without cranial features of GCA have so low a risk of vasculitis that a temporal artery biopsy could be initially avoided.[67] Patients with isolated GCA or GCA associated with polymyalgia rheumatica have similar characteristics.[68]

LABORATORY FINDINGS

Erythrocyte sedimentation rate is usually higher than 50 mm/hour,[1 2] but a lower erythrocyte sedimentation rate is possible.[69 70] An erythrocyte sedimentation rate lower than 50 mm/hour is present in about 5% of patients with GCA.[69 70] However, a completely normal erythrocyte sedimentation rate (lower than 30 mm/hour) seems to be exceptional.[69 70] C-reactive protein and fibrinogen are usually raised. Anaemia of chronic disease, thrombocytosis, and raised liver enzymes levels are frequent.[1 2 14 15] Thrombocytosis (platelet count higher than 400×10^9/l) in patients suspected of having GCA seems to have a high specificity and positive predictive value in the diagnosis of GCA.[71]

Previous studies have suggested that the circulating CD8 T-cells are reduced in patients with active GCA.[72] However, these findings have not been confirmed,[73] and the utility of this parameter needs to be re-evaluated. Levels of interleukin-6 appear to be a sensitive indicator of active GCA,[74] but the availability of this measurement is limited. Anticardiolipin antibodies are detected in patients with GCA and may function as reactive antibodies in relation to endothelial lesions.[75] However, one study has reported that serum IgG anticardiolipin antibodies levels are useful in the detection of flares and relapses in GCA.[76]

DIAGNOSIS

GCA should be confirmed by temporal artery biopsy.[77] Biopsy demonstrates a vasculitis characterised by a predominance of mononuclear infiltrates or granulomas, usually with multinucleated giant cells. A normal temporal artery biopsy does not exclude GCA since the lesions are skipped. Long specimens (higher than 20 mm) may be more likely to yield a positive result.[78] Routinely examining a temporal artery biopsy at multiple levels seems not to increase the diagnostic yield, although selective further examination may be indicated in some cases.[79] Gabriel *et al* described that the absence of jaw claudication or temporal artery abnormalities on examination, and the presence of synovitis or a lower erythrocyte sedimentation rate predict a highly likely of a negative biopsy.[80] González-Gay *et al* also suggested that patients without visual manifestations, temporal artery abnormalities on examination, or constitutional syndrome have a low risk of having a positive biopsy.[81] Unilateral temporal artery biopsy may be sufficient to exclude the diagnosis of GCA in patients with a low clinical suspicion.[82] However, contralateral temporal artery biopsy should be considered in patients with a high clinical suspicion of GCA and a negative first biopsy.

The American College of Rheumatology proposed a list of criteria for diagnosis of GCA (box 1).[39] The presence of three or more criteria had a sensitivity of 97.5% and a specificity of 78.9% in a French study of patients in whom the diagnosis of GCA was confirmed or ruled out by temporal artery biopsy.[83]

Box 1: The American College of Rheumatology criteria for diagnosis of giant cell arteritis

- Age at onset ⩾50 years.
- New headache.
- Temporal arteries abnormalities.
- Erythrocyte sedimentation rate ⩾50 mm/hour.
- Positive temporal artery biopsy (vasculitis characterised by a predominance of mononuclear infiltrates or granulomas, usually with multinucleated giant cells).

The presence of a halo sign or an inflammatory stenosis on colour duplex ultrasonography of the temporal arteries may predict which patients will need biopsy and eliminate patients who would not benefit from biopsy.[84] It has been suggested that the lack of a halo sign can in practice rule out a GCA.[84 85] However, ultrasonography seems not to improve the diagnostic accuracy of a careful physical examination.[86] Positron emission tomography may contribute to the non-invasive diagnosis of GCA, and to the evaluation of the extent of disease, response to treatment, and disease recurrence, although confirmatory studies are necessary.[87] A high temporal 67-gallium uptake is observed in patients with GCA, and this uptake normalises during remission.[88]

TREATMENT

Steroids are the treatment of choice for GCA.[1 2 89 90] The initial and maintenance dose, the rate of reduction of the dose, and the total duration of steroid therapy are controversial. There is no definitive evidence about these questions. The usual initial dose is 40–60 mg of prednisone per day or its equivalent and the response is rapid: a few days. Steroid resistance is a risk factor for GCA complications. Gradual tapering after 1–2 months of treatment should be tried.[89 90] The objective would be to reach a maintenance dose of 7.5–10 mg per day or lower. However, relapse is frequent during steroid tapering.[90] One retrospective evaluation studied different steroid regimens and showed that a starting dose of 30–40 mg per day of prednisone tapering to 10 mg per day within six months and to 5–7.5 mg per day within one year was effective and less toxic than higher dose regimens.[91] A strong initial systemic inflammatory response (characterised by fever, weight loss, erythrocyte sedimentation rate ⩾85 mm/hour, and/or anaemia) may be associated with higher and more prolonged steroid requirements.[92]

Assessment of symptoms and signs, erythrocyte sedimentation rate, and C-reactive protein level are the most useful data in monitoring.[1 2 89] Stopping steroid therapy after two years may be reasonable,[89] although repeated temporal artery biopsy has shown evidence of active disease even after nine years of steroid therapy.[93] Steroid response is similar in patients older than 75 years, although rheumatic side effects are more frequent.[94] An initial intravenous pulse of methylprednisolone has no significant long term, steroid sparing effects in the treatment of simple forms of GCA.[95] Evolving ischaemic strokes have been reported after steroid therapy, usually within the vertebrobasilar territory.[96]

Visual loss due to GCA treated with intravenous or oral steroids improves only in a few patients.[97–99] Data indicate that there is a better chance of visual improvement with early diagnosis and an immediate start of steroid therapy.[42 97–99] Intravenous steroids may offer a greater prospect of improvement,[97] although the results are contradictory.[98 100] In suspected cases of GCA, to begin steroid treatment before confirmatory temporal artery biopsy may be justified to prevent complications. Moreover, temporal artery biopsy is useful several weeks after institution of steroids.[101 102]

Calcium and vitamin D supplements must be provided to all patients treated with steroids. Bisphosphonate therapy should be considered in patients with osteoporosis.[103] It has been suggested that the bone mass loss due to deflazacort is lower than the loss due to prednisone. However, deflazacort did not result in less bone loss than prednisone in patients with GCA in a recent study.[104]

Methotrexate may be useful to control disease activity or to decrease the dose of steroids.[105] In a Spanish trial, treatment with prednisone and methotrexate reduced the proportion of patients who experienced at least one relapse or multiple relapses, and the mean cumulative dose of prednisone was lower in the patients with combined therapy.[106] However, other studies have not confirmed these results, although they used different therapeutic schemes.[107 108] There is evidence in animal studies of the complementary action of acetylsalicylic acid and steroids in suppressing proinflammatory cytokines in the vascular lesions of GCA.[109] Infliximab and etanercept, antitumour necrosis factor agents, have been successful in the treatment of some cases of GCA.[110 111]

PROGNOSIS

The mortality of treated patients with GCA does not seem to be increased,[112–114] probably due to a correct diagnosis and management. However, death due to cardiovascular disease may be increased in patients with GCA, related to either the steroid therapy itself or insufficient control of inflammation.[115] In a French study, long term survival was better in patients with no initial ocular manifestations and in patients who could take less than 10 mg per day of prednisone at six months.[116] Steroid treatment in patients with GCA may cause morbidity and mortality, more commonly due to fractures and infections.[117] It has been suggested that the prevalence of cancer is increased in patients with GCA.[118 119] However, a recent study found no differences in frequency of malignant neoplasms between patients with GCA and population controls.[120]

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